PATENT COOPERATION TREATY

Bilag

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To.
NOVO NORDISK A/S
Novo Allé
DK-2880 Bagsvaerd
DENMARK

Reference
Country
Agent
11. FEB. 2005
Short title
Action
Term

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 6815-WO	Date of mailing *(day/month/year)* 09/02/2005 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/DK2004/000181	International filing date *(day/month/year)* 18/03/2004
Applicant NOVO NORDISK A/S	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Joëlle Gerber

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by canceling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim ■ cancelled;

(iii) the claim is new,

(iv) the claim replaces one or more claims as filed,

(v) the claim is the result of the division of a claim as filed

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1 [Where originally there were 48 claims and after amendment of some claims there are 51]
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged, new claims 49 to 51 added."

2 [Where originally there were 15 claims and after amendment of all claims there are 11]
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where onginally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]
"Claims 1 to 6 and 14 unchanged, claims 7 to 13 cancelled; new claims 15, 16 and 17 added " or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added, all other claims unchanged."

4 [Where various kinds of amendments are made]
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14, claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added "

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be bnef, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
6815-WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/DK2004/000181	18/03/2004	18/03/2003
Applicant		
NOVO NORDISK A/S		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No I.

2. [X] **Certain claims were found unsearchable** (See Box II).

3. [X] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK2004/000181

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/36 A61J1/06 A61P7/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X Y	US 6 310 183 B1 (JOHANNESSEN MARIE ET AL) 30 October 2001 (2001-10-30) column 5 - column 7; claims	1-62 1-62
Y	WO 99/66031 A (MATTHIESSEN PETER ; BAXTER AG (AT); TURECEK PETER (AT); SCHWARZ HANS P) 23 December 1999 (1999-12-23) the whole document	1-62
X	WO 03/007868 A (FOSTER PETER REYNOLDS ; MCINTOSH RONALD VANCE (GB); COMMON SERVICES AG) 30 January 2003 (2003-01-30) the whole document	63-67

-/--

[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 January 2005	09/02/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Bayrak, S

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Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	EP 1 232 753 A (CHUGAI PHARMACEUTICAL CO LTD) 21 August 2002 (2002-08-21) page 2, line 2 - page 3, line 30 page 5, line 15 - line 45 page 11, line 54 - line 57; claims	63-67
P,X	WO 03/055512 A (JENSEN MICHAEL BECH ; KORNFELT TROELS (DK); NOVO NORDISK AS (DK); HANS) 10 July 2003 (2003-07-10) cited in the application the whole document	1-62
P,X	WO 03/055511 A (JENSEN MICHAEL BECH ; KORNFELT TROELS (DK); NOVO NORDISK AS (DK); HANS) 10 July 2003 (2003-07-10) the whole document	1-62

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-62

   A liquid, aqueous pharmaceutical composition comprising Factor VII, a buffering agent (pH5-9) and calcium ions wherein the molar ration of non-complexed calcium ions to the Factor VII polypeptide is lower than 0.5 and its use for therapy.

   ---

2. claims: 63-67

   A container for a liquid, aqueous pharmaceutical composition comprising Factor VII.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK2004/000181

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 62 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos..
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3 [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK2004/000181

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6310183 B1	30-10-2001	US 2002115590 A1	22-08-2002
WO 9966031 A	23-12-1999	AT 408613 B	25-01-2002
		AT 104398 A	15-06-2001
		WO 9966031 A2	23-12-1999
		AU 758152 B2	13-03-2003
		AU 4353399 A	05-01-2000
		EP 1133555 A2	19-09-2001
		JP 2002518411 T	25-06-2002
		US 6777390 B1	17-08-2004
WO 03007868 A	30-01-2003	EP 1416899 A1	12-05-2004
		WO 03007868 A1	30-01-2003
		US 2004199138 A1	07-10-2004
EP 1232753 A	21-08-2002	AU 6875900 A	10-04-2001
		EP 1232753 A1	21-08-2002
		WO 0117542 A1	15-03-2001
WO 03055512 A	10-07-2003	BR 0215216 A	16-11-2004
		BR 0215218 A	16-11-2004
		CA 2470313 A1	10-07-2003
		CA 2470511 A1	10-07-2003
		WO 03055511 A1	10-07-2003
		WO 03055512 A1	10-07-2003
		EP 1458407 A1	22-09-2004
		EP 1458408 A1	22-09-2004
		US 2004043933 A1	04-03-2004
		US 2004037893 A1	26-02-2004
WO 03055511 A	10-07-2003	BR 0215216 A	16-11-2004
		BR 0215218 A	16-11-2004
		CA 2470313 A1	10-07-2003
		CA 2470511 A1	10-07-2003
		WO 03055511 A1	10-07-2003
		WO 03055512 A1	10-07-2003
		EP 1458407 A1	22-09-2004
		EP 1458408 A1	22-09-2004
		US 2004043933 A1	04-03-2004
		US 2004037893 A1	26-02-2004

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day.month.year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK2004/000181	18.03.2004	18 03.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/36, A61J1/06, A61P7/04

Applicant
NOVO NORDISK A/S

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No IV Lack of unity of invention
- ☒ Box No V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2 **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later

For further options, see Form PCT/ISA/220

3 For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA

European Patent Office - P B 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel +31 70 340 - 2040 Tx 31 651 epo nl
Fax. +31 70 340 - 3016

Authorized Officer

Bayrak, S

Telephone No. +31 70 340-3263

Box No. I Basis of the opinion

1 With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2 With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a type of material:

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material:

☐ in written format

☐ in computer readable form

c. time of filing/furnishing:

☐ contained in the international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☐ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-67 (all partially)

because:

☒ the said international application, or the said claims Nos. 62 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos 1-67 (all partially; see separate sheet)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-67
Inventive step (IS)	Yes:	Claims	
	No	Claims	1-67
Industrial applicability (IA)	Yes:	Claims	1-61,63-67
	No:	Claims	62 (see separate sheet)

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Re item III
Non-establishment of opinion

1. Claim 62 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2. Present claims 1-67 relate to an extremely large number of possible compounds or to a compound defined by reference to a desirable characteristic or property ("..wherein the molar ratio of non-complexed calcium ions to the Factor VII polypeptide is lower than 0.5", "buffering agent", "stabilising agent", "metal-containing agent..", "non-ionic surfactant", "tonicity modifying agent", "antioxidant", "preservative", "factor VII sequence variant"). In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which clearly specified the compounds in the description, examples or the claims.

No opinion will be given in respect of subject matter which is not covered by the search report (Rule 66.1(e)PCT)

Re Item IV.

This Authority considers that there are 2 separate inventions/groups of invention covered by the claims indicated as follows:

1-62
A liquid, aqueous pharmaceutical composition comprising Factor VII, a buffering agent (pH5-9) and calcium ions wherein the molar ration of non-complexed calcium ions to the Factor VII polypeptide is lower than 0.5; and its use for therapy.

63-67
A container for a liquid, aqueous pharmaceutical composition comprising Factor VII.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem to be solved by the present invention is:

(i) provision of a pharmaceutical composition comprising Factor VII that can be stored and administered as a liquid

(ii) provision of a container to allow stable storage of a liquid pharmaceutical composition of Factor VII.

The concept of provision of a liquid, aqueous pharmaceutical composition comprising Factor VII represents the technical features which may, a priori, unify the subjects mentioned above.

Document D1 discloses a liquid formulation of Factor VII (Factor VIIa)(see passages cited in the search report).

Consequently, the idea of a liquid, aqueous pharmaceutical composition comprising Factor VII in the state of the art is known and cannot serve as a single general inventive concept linking a pharmaceutical composition comprising Factor VII that can be stored and administered a s a liquid (and its therapeutic use) with a container which allows stable storage of a liquid pharmaceutical composition of Factor VII, which have no special technical features in common.

In the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention, and the different solutions not belonging to a common inventive concept are identified as the different subjects listed above. Each of the inventions listed is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

An opinion is given on the first subject (claims 1-62) and second subject (claims 63-67) mentioned.

Re Item V

1 The following documents are referred to in this communication:
D1 : US6310183
D2 : WO9966031
D3: WO 03007868
D4: EP-A-1 232 753

NOVELTY (Art. 33(2) PCT)

1.1 The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of the independent claims 1,57,60-62 is not new in respect of the prior art as defined in the regulations (Rule 64(1)-(3) PCT):

1. Document D1 discloses a method and a liquid, aqueous pharmaceutical composition comprising a Factor VII polypeptide (Factor VIIa) and a buffering agent suitable for keeping pH in the range preferred of from about 5-7.5 and more preferred pH 5-6 containing calcium ions (calcium chloride) and other excipients (such as stabilising agents, modifying agents, antioxidants etc.) as mentioned in the dependent claims; and its use for treating a Factor VII-responsive syndrome.

The applicants attention is drawn to the fact that it cannot be excluded that in the said composition the molar ratio of non-complexed calcium ions to the Factor VII polypeptide is lower than 0.5.

Therefore, the subject matter of the independent claims 1,57,60-62 is not new (Article 33(2) PCT).

2. Document D3 discloses a silica coated glass container and document D4 discloses a container coated with cycloolefin polymers suitable for the storage of a liquid, aqueous pharmaceutical composition comprising a Factor VII polypeptide as in claims 1-56 (see passages cited in the search report).

Therefore, the subject matter of the independent claim 63 is not new (Article 33(2) PCT).

2 **INVENTIVE STEP (Art. 33(3) PCT)**

2.1 Even if novelty could be established, the present application would not meet the requirements of Art. 33(3) PCT. In view of documents D1 and D2 (D2 see

whole document) the subject-matter of the independent claims 1,57,60,61,62 does not involve an inventive step in the sense of Art. 33(3) PCT. Liquid, aqueous pharmaceutical composition comprising Factor VII polypeptide appear well known in the state of the art.

2.2 In view documents D3 and D4 the subject-matter of the independent claim 63 does not involve an inventive step in the sense of Art. 33(3) PCT. Container suitable for the stable storage of liquid, aqueous pharmaceutical composition comprising Factor VII polypeptide appear well known in the state of the art.

3 DEPENDENT CLAIMS

The dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see documents (D1-D4) and the corresponding passages cited in the search report.

4 INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

4.1 Claims 1-61,63-67 fulfil the requirements of (Art. 33(4) PCT)

4.2 For the assessment of the present claim 62 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.